

10/588940

* NOTICES *

IAP11 Rec'd PCT/PTO 08 AUG 2006

JPO and NCIPPI are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.

2. **** shows the word which can not be translated.

3. In the drawings, any words are not translated.

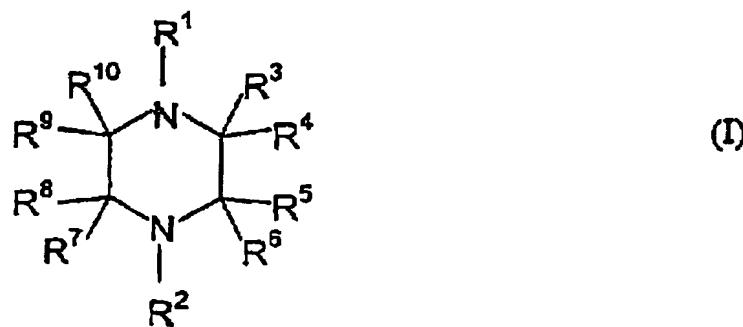
CLAIMS

[Claim(s)]

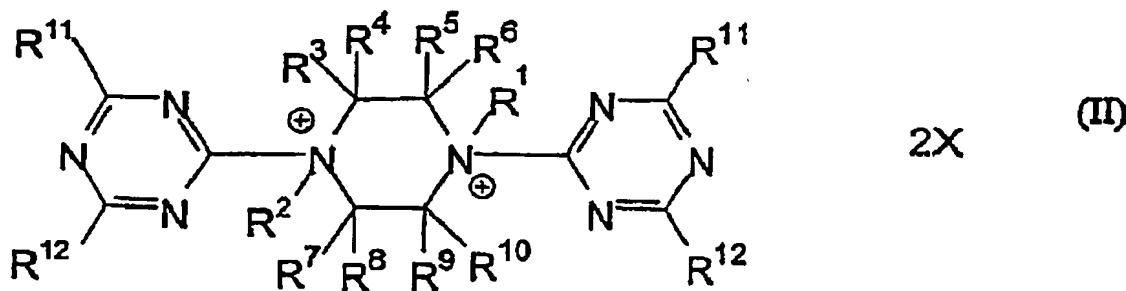
[Claim 1]

An amide or ester is set to the approach of manufacturing under existence of an organic solvent from a carboxylic acid and an amine component, or an alcoholic component depending on the case under existence of a 1,3,5-triazine and tertiary amine, or triazine-amine addition product, and it is a general formula I as tertiary amine.

[Formula 1]



The ring type diamine come out of and shown (2), or from now on, it will be a general formula II.
 [Formula 2]



Among the [above-mentioned type, R1 and R2 express CH₃, respectively, or become one clue and express -(CH₂)₂-p-oxo. R3-R12 Methoxy and ethoxy ** propoxy, butoxy one, phenoxy, or aryl is expressed especially. mutually-independent -- =H, C₁-10-alkyl, and C₁ - C₁₀-alkoxy ** -- 2X one or more anions -- advantageous -- halogenide ion, for example, Cl⁻, and Br⁻ Are shown by] showing I-,

HSO₄⁻, a sulfate anion, or an organic carboxylate anion. The manufacturing method of the amide or ester characterized by using the addition product formed by becoming together with a triazine component or Compound I, and/or the mixture of the arbitration of II.

[Claim 2]

as a carboxylic-acid component -- amino acid -- advantageous -- an enantiomer -- pure amino acid and its derivative -- For example, the inside of the peptide which has at least one isolation carboxyl group and by which N protection was carried out, and a general formula R-COOH[type, R -- a case -- one -- a piece -- more than -- C -- one - ten - alkyl -- C -- one - 17 - alkyl -- and -- C -- three - 14 - cycloalkyl -- permuting -- having had -- C -- six - 14 - aryl -- it is --] -- being shown -- having -- a carboxylic acid -- using it -- being according to claim 1 -- an approach .

[Claim 3]

as an amine component -- amino acid -- advantageous -- an enantiomer -- pure amino acid and its derivative -- For example, the amino acid which has at least one isolation amino group, respectively and by which N protection was carried out or the peptide by which C protection was carried out, Or it is the approach according to claim 1 or 2 of using the compound shown by general formula R-NH₂ [the inside of a formula and R are C6 permuted by one or more C1 - 10-alkyls, C1 - 17-alkyl, and C3 - 14-cycloalkyl depending on the case - 14-aryl].

[Claim 4]

An approach given in any 1 term to claims 1-3 which uses the 1,3,5-triazine component by which the Krol permutation was carried out.

[Claim 5]

An approach given in any 1 term to claims 1-4 which uses 2-chloro -4 and 6-dimethoxy-1,3,5-triazine (CDMT) as 1,3,5-triazine.

[Claim 6]

An approach given in any 1 term to claims 1-5 which uses the N and N'-dimethyl -1 and 4-piperazine as ring type diamine.

[Claim 7]

An approach given in any 1 term to claims 1-5 which uses a diazabicyclo [2.2.2] octane (DABCO) as 2 ring type diamine.

[Claim 8]

A carboxylic-acid component is inserted in and it is an approach given in ring type diamine, a triazine component, and any 1 term to claims 1-7 that finally adds an amine component or an alcoholic component succeedingly.

[Claim 9]

An approach given in any 1 term to claims 1-8 which reacts at the temperature of -5-+25 degrees C advantageously especially -20-+40 degrees C -80-+150 degrees C.

[Claim 10]

An approach given in any 1 term to claims 1-9 which carries out a reaction under existence of the mixture of arbitration which consists of an organic solvent, for example, a tetrahydrofuran, the methyl-third butyl ether, ethyl-acetate ester, a halogenation solvent, for example, dichloromethane, or these.

[Claim 11]

An approach given in any 1 term to claims 1-10 which has especially the stoichiometric ratio of ring type diamine and a triazine component between 0.47-0.53 advantageously between 0.30-0.75 between 0.30-1.10.

[Claim 12]

The approach given [a ratio with a carboxylic acid, an amine component, or an alcoholic component] in 0.2-5.0, and any 1 term to claims 1-11 that are 0.80-1.20 advantageously.

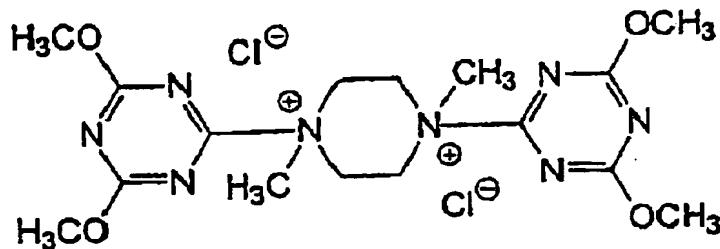
[Claim 13]

The approach given [the mole ratio of a carboxylic acid and a triazine component] in 0.5-1.5, and any 1 term to claims 1-12 that are 0.95-1.0 advantageously.

[Claim 14]

Formula (III)
[Formula 3]

(III)



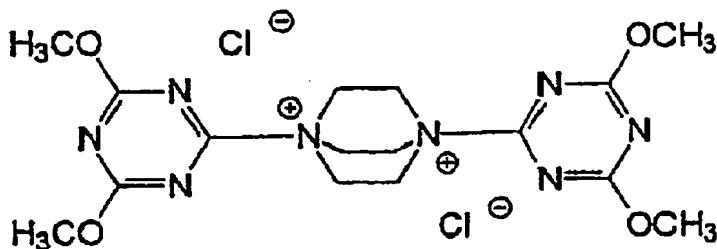
An approach given in any 1 term to claims 1-13 which comes out and uses the addition product shown.

[Claim 15]

Formula (V)

[Formula 4]

(V)

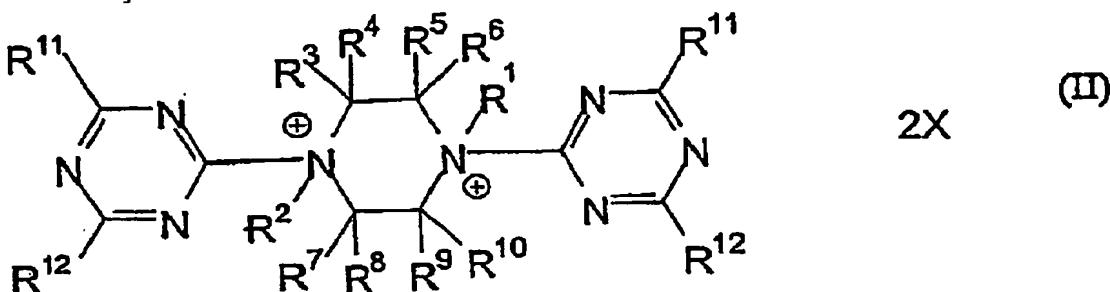


An approach given in any 1 term to claims 1-13 which comes out and uses the addition product shown.

[Claim 16]

Formula (II)

[Formula 5]

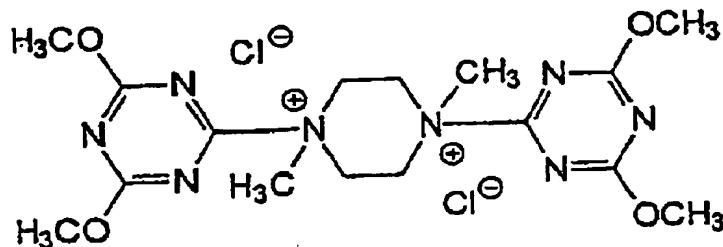


[-- a formula -- inside -- R -- one - R -- 12 -- mutually-independent -- = -- H -- C -- one - ten - alkyl -- C -- one - C -- ten - alkoxy one -- ** -- especially -- methoxy -- ethoxy -- ** -- propoxy one -- butoxy one - - phenoxy -- or -- aryl -- expressing -- and -- two -- X -- one -- a piece -- more than -- an anion --

advantageous -- a halogenide -- ion -- for example, -- Cl - Br - I - or -- HSO -- four - or -- sulfate -- an anion -- or -- organic -- carboxylate -- an anion -- expressing --] -- be shown -- having -- a compound . [Claim 17]

Formula (III)

[Formula 6]

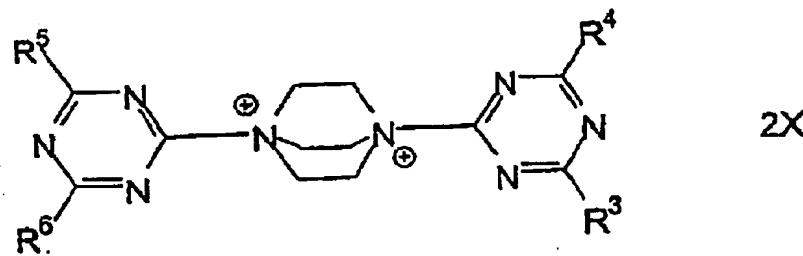


The compound according to claim 15 come out of and shown.

[Claim 18]

General formula (IV)

[Formula 7]

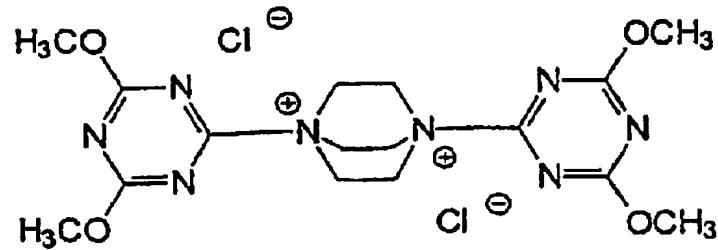


[-- a formula -- inside -- R -- one - R -- four -- mutually-independent -- = -- H -- C -- one - ten - alkyl -- C -- one - C -- ten - alkoxy one -- ** -- especially -- methoxy -- ethoxy -- ** -- propoxy one -- butoxy one -- phenoxy -- or -- aryl -- expressing -- and -- two -- X -- one -- a piece -- more than -- an anion -- advantageous -- a halogenide -- ion -- for example, -- Cl - Br - I - or -- HSO -- four - or -- sulfate -- an anion -- or -- organic -- carboxylate -- an anion -- expressing --] -- be shown -- having -- a compound .

[Claim 19]

Formula (V)

[Formula 8]



The compound according to claim 18 come out of and shown.

[Translation done.]

IAP11 Rec'd PCT/PTO 08 AUG 2006

* NOTICES *

JPO and NCIPi are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

The object of this invention is the manufacturing method of an amide or ester.

[0002]

The approach for manufacturing the amide or ester which was generally established and was indicated by the publication at the detail Using at least 1Eq of 1,3,5-triazine as a coupling reagent Coupling of a carboxylic acid, an amine, or the alcohol is carried out. [Z. which is changing into a desirable amide or ester J. Kamiński and Tetrahedron Lett.1985, 26, and 2901-2904; Z. J.Kamiński and Synthesis 1987 917-920; L.Alig et.al. and EP 0381033, 1990; P.A.Hipkiss et.al., J.Org.Chem.1995, 60, 7033-7036; E.C.Tayloret.al., J.Org.Chem.1996, 61, and 1261-1266]. In this case, it became clear that 2-chloro -4 and 6-dimethoxy-1,3,5-triazine (CDMT) were triazine components with the highest effectiveness.

Additionally, in the case of this approach, existence of the stoichiometric quantities (at least 1Eq) of the base in the form of tertiary amine is needed, and a ***** N-methyl morpholine is used in that case.

[0003]

It is the molar quantity of the magnitude (for example, 1,3,5-triazine or tertiary amine) of this ** to a part for mol ** of the component for which the concept of the "equivalent" is used in relation to count of the theoretical yield of an amidation object in relation to this according to the definition, or when the component relevant to count of the theoretical yield of an amidation object contains many reactant functional groups (in for example, the case of dicarboxylic acid), it is the molar quantity of a reactant functional group.

[0004]

The above-mentioned approach having produced the desirable product in good yield thru/or very good yield, and having already achieved success about much various use was indicated. namely, -- above all -- this approach -- pharmaceutical -- an important amide -- a peptide and ester can be obtained especially. As a carboxylic acid, it is N because of peptide synthesis. - The protected amino acid or C terminal peptide can be used, and the amino acid or amino terminal peptide by which carboxyl protection was carried out typically is used as an amine.

[0005]

Coupling of such a carboxylic acid or an amine produces the industrial especially important joint kind of a peptide, therefore this coupling approach is learned widely, and it has advanced importance commercially. [M.Kunishima et.al., Tetrahedron 1999, 55, and 13159-13170] which can use the addition product which ****s from these two components instead of 1,3,5-triazine and tertiary amine -- however, this needs an additional separation process. [moreover,]

[0006]

however, said approach has some serious faults in spite of the use proved variously within the limits of amide composition and peptide synthesis, or ester composition : namely, molecular weight with comparatively high N-methyl morpholine of the base usually used -- having -- ****ing -- a lot of amounts of trash -- imitating -- **. Therefore, probably, use of the tertiary amine which has low

molecular weight will be desirable from the atomic reason and the atomic ecological view of economical efficiency in the case of industrial use because of the amount of trash which especially decreased essentially by it. However, no trials using the base of molecular weight low until now achieve success in a regrettable thing freely.

[0007]

: which can find out another fault of an old approach in an after-treatment phase -- although the hydrochloride formed from tertiary amine is actually dissolved underwater mainly, it also has the remarkable solubility in the inside of an organic solvent. Although the remarkable solubility in the inside of this organic solvent can actually be decreased by introducing making dihydrochloride form the 2nd ionic charge into a tertiary amine molecule,; however this can need existence of the 2nd base functional group, and this 2nd base functional group can be made to protonate in an acidic solution by the it side in this case in the case of shaking. However, this imitates the load of the economical efficiency of the amount of trash already indicated again, and an atom by installation of other base functional groups increasing the molecular weight of a base, and it is **.

[0008]

Moreover, it is desirable to also often improve unsuitable yield for industrial processing with less than 90% of value.

[0009]

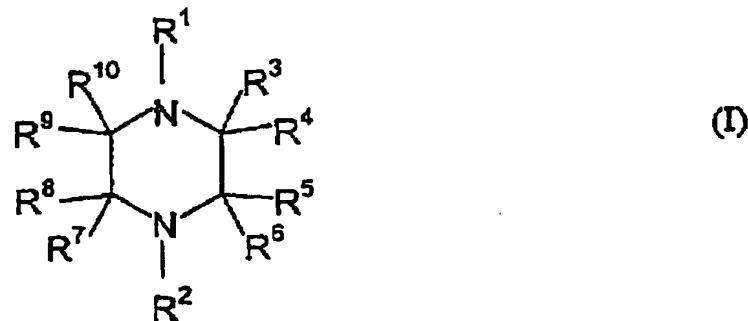
Therefore, the approach of manufacturing an amide or ester under existence of an organic solvent from a carboxylic acid and an amine component, or an alcoholic component depending on the case under existence of 1,3,5-triazine and tertiary amine was developed, and at that time, the technical problem that it had only low molecular weight was imposed as additional tertiary amine was made per [which is used] one mol of 1,3,5-triazine. The base should contain two base functional groups for the total mass of N-methyl morpholine for which the total mass of the tertiary amine used was ***** used especially until now the circumference of the bottom remarkably. Furthermore, high yield should be able to be attained by still shorter reaction time using the new coupling system.

[0010]

This technical problem is a general formula I as tertiary amine.

[0011]

[Formula 9]

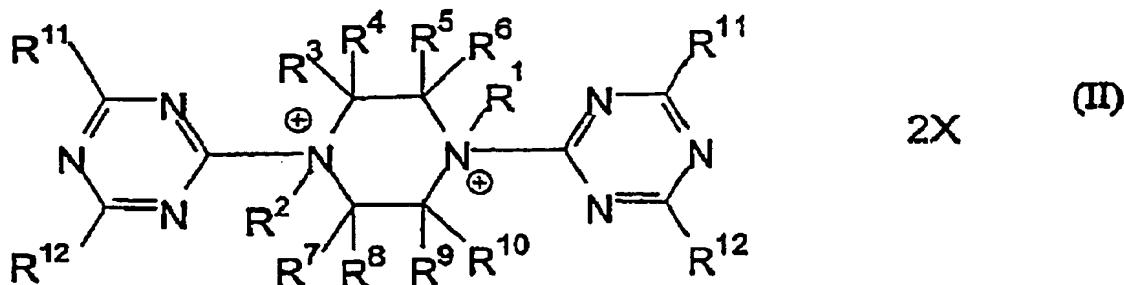


[0012]

The ring type diamine come out of and shown (2), or from now on, it will be a general formula II.

[0013]

[Formula 10]



[0014]

Among the [above-mentioned type, R1 and R2 express CH₃, respectively, or become one clue and express -(CH₂)₂-pons. R₃-R₁₂ C₁ permuted by one or more C₁ - 10-alkyl groups mutually-independent depending on =H and the case - 10-alkyl, C₅ - 30-aryl are expressed especially. C₁ - C₁₀-alkoxy ** -- especially -- methoxy and ethoxy ** propoxy, butoxy one, phenoxy, or aryl -- 2X one or more anions for a charge balance -- advantageous -- halogenide ion -- For example, Cl⁻, Br⁻, I⁻ or HSO₄⁻, a sulfate anion, It is solved by the approach of using the addition product formed by becoming together with the triazine component shown by] showing an organic carboxylate anion, for example, an acetic-acid anion, a propionic-acid anion, or a benzoic-acid anion or Compound I, and/or the mixture of the arbitration of II.

[0015]

For this invention which becomes together with 1,3,5-triazine and has the 3rd amino group in an unexpected thing, respectively, use of essential (2) ring type diamine is made to act as an outstanding coupling system in the case of this approach, and produces an amide or ester in it in the very good quantitative yield which is, carries out and generally exceeds 80%. In this case, a desirable product can be obtained from a well-known technical level at the high formation rate which exceeds a well-known formation rate remarkably. In this case, a ring type diamine component essential (2) to an unexpected thing for this invention can also be used by stoichiometric ullage. (2) Even if it is the case where 0.5Eq of ring type diamines is only used, a reaction advances still more nearly remarkably effectively.

[0016]

Moreover, though it can think as intermediate field which have the charge and chemical property from which many possible diamine-triazine addition products differ in a very unexpected thing for the two functionality of ring (2) type diamine, a reaction goes smoothly with high yield.

[0017]

Selection of a carboxylic acid contains the carboxylic acid of all classes rather than is limited to monocarboxylic acid. Advantageously a reaction Namely, amino acid, for example, the alpha-amino acid, and beta-amino acid, The inside of the peptide which has advantageously the amino acid of enantiomer purity, the amino acid by which N protection was carried out, and at least one isolation carboxyl group and by which N protection was carried out, and a general formula R-COOH[type, R -- a case -- one -- a piece -- more than -- C -- one - ten - alkyl -- C -- one - 17 - alkyl -- and -- C -- three - 14 - cycloalkyl -- permuting -- having had -- C -- six - 14 - aryl -- it is --] -- being shown -- having -- a carboxylic acid -- use -- the time -- very -- effective -- succeeding . (Tertiary butyl)-phenyl is indicated as R in instantiation.

[0018]

As an amine component, the amine of all classes can be used similarly. Especially this approach advantageously Formal amino acid, for example, the alpha-amino acid, and beta-amino acid of enantiomer purity, The amino acid which has at least one isolation amino group, respectively and by which C protection was carried out or the peptide by which C protection was carried out as an amine component, Or it is suitable when using the compound shown by general formula R-NH₂ [the inside of

a formula and R are C6 permuted by one or more C1 - 10-alkyls, C1 - 17-alkyl, and C3 - 14-cycloalkyl depending on the case - 14-aryl].

[0019]

All the compounds that have isolation hydroxyl can be used as an alcoholic component.

[0020]

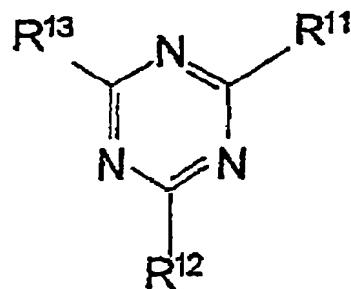
Therefore, especially this approach is suitable also for leaving the ***ing suitable carboxylic-acid component and amine component, and manufacturing a peptide by association of peptide linkage within the limits of a condensation reaction. C-end peptide which has N-end peptide which has an amino functional group and the protected carboxyl functional group or an isolation carboxyl functional group, and the protected amino functional group as such a thing functions. This reaction advances effectively in relation to the rate of formation, and a formation rate especially. In this case, racemization which produces a common coupling reagent, for example, the serious problem in the case of dicyclohexylcarbodiimide (DCC), does not happen.

[0021]

A 1,3,5-triazine component is 1,3,5-triazine by which the Krol permutation was carried out advantageously, and is the following general structure expression. :

[0022]

[Formula 11]



[0023]

It has [among a formula, advantageously, N (alkyl)2, Cl, and Br to O-alkyl in which radicals R11 and R12 have a carbon atom to 14 pieces independently, respectively, O-aryl which has OCH3, OC2H5, and a carbon atom to 14 pieces, the alkyl which has a carbon atom to 14 pieces, and 18 pieces are expressed, and R13 expresses Cl].

[0024]

As a suitable 1,3,5-triazine component, 2-chloro -4 and 6-dimethoxy-1,3,5-triazine (CDMT) are especially prepared in this invention. However, a reaction is successful also when using another derivative which has 1,3,5-triazine fragmentation, 2 [for example,], and 4-dichloro-6-methoxy-1,3,5-triazine, or cyanuric chloride.

[0025]

as ring type diamine which has the 3rd two amino group, advantageously, although the N and N'-dimethyl -1 and 4-piperazine are used, this compound kind of another example of representation, for example, 2 ring type diazabicyclo [2.2.2] octane, (DABCO), 1, and 4-diethyl piperazine is very suitable for this invention -- a certain thing became clear.

[0026]

A coupling reaction is usually carried out by carrying out a carboxylic acid under existence of triazine and (2) ring type diamine together with an amine or alcohol, respectively. Preferably, a carboxylic acid is inserted in, the ring type diamine which has the 3rd two amino group next (2) is added, and the triazine component used successingly, respectively is added. Finally, an amine component or an alcoholic component is added. However, the sequence of addition does not need to be decided by this

sequence. Rather, implementation of a reaction is possible also in order of the arbitration of addition of each component.

[0027]

-80 degrees C - +150 degrees C of -20 degrees C - +40 degrees C of reactions are advantageously carried out especially advantageous in the case of this approach with the reaction temperature of -5 degrees C - 25 degrees C.

[0028]

Moreover, it is prepared in this invention that a reaction can be carried out under existence of the mixture of arbitration which consists of an organic solvent, for example, a tetrahydrofuran, the methyl-third butyl ether, acetic-acid ethyl ether and a halogenated solvent, for example, dichloromethane, and these.

[0029]

Typically, depending on the chloro content of a triazine component, the ratio of a carboxylic acid and a triazine component is successful [as for a reaction] the best, when it is 0.95-1.0 advantageously, 0.50-1.50, and the carboxylic acid of a reaction component and an amine, or an alcoholic component can fully be used for stoichiometric within the limits of [large] 0.2-5.0, and is natural in this case --; with the desirable ratio of 0.80-1.20 -- however, one in these two reaction components may be used with an excessive amount. (2) the ratio of ring type diamine and a triazine component -- 0.30-1.10 -- especially -- 0.30 to 0.75 -- it is the value of 0.47-0.53 especially advantageous.

[0030]

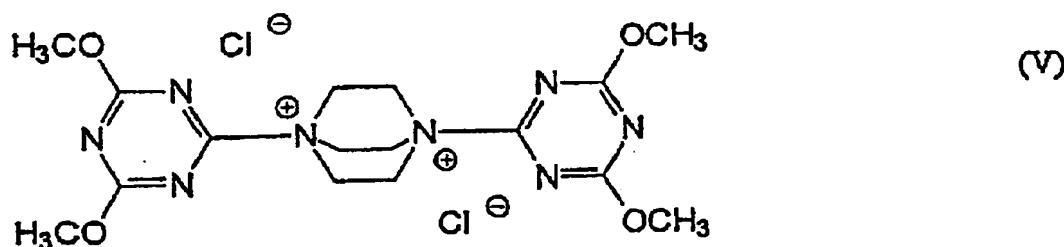
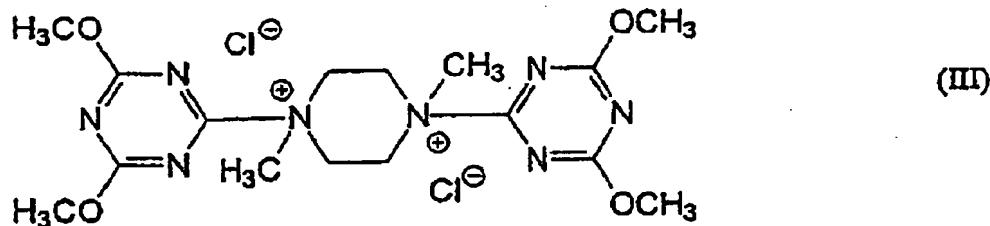
As mentioned above, the addition product alternatively separated from these two components instead of addition of 1,3,5-triazine and (2) ring type diamine depending on the case where it is formed can be added, and this is considered like this invention (refer to Formula II and IV).

[0031]

In this case, according to this invention, it became clear that the addition product which has the following special formulas III and V especially is effective. :

[0032]

[Formula 12]



[0033]

Moreover, this invention is asked for protection of a patent of the compound of formula (II)- (V) with the manufacturing method.

[0034]

(2) The coupling system newly found out while only using the half-stoichiometric content and the stoichiometric content of 1,3,5-triazine advantageous [***** 3 diamine] enables manufacture of an amide or a peptide with the high yield to 100%. This yield not only exceeds the result from a well-known technical level, but essentially guarantees few amounts of trash. That is, while N-methyl morpholine uses it by the well-known technical level, in taking the same yield, about 2 times [in use by this invention of the N and N'-dimethyl -1 and 4-piperazine] trash arises. The amount of trash decreases further absolutely as compared with a well-known technical level. It, that is, the yield attained by this invention are because it is still higher.

[0035]

Therefore, speaking in the gross, this invention's having the following advantage. :

(a) Compare with a well-known technical level and it is high yield.

[0036]

(b) Short reaction time, it, that is, a reaction are because it has already ended 1 hour after.

[0037]

(c) Few [clearly] amounts of trash of a tertiary amine base are measured with a well-known technical level (generally less than 50, 60%).

[0038]

(d) Separation by which the product by the possibility of the formation of a bis-hydrochloride connected with the improved water solubility has been improved.

[0039]

This invention is asked for protection of a patent of the approach of manufacturing an amide or ester under existence of an organic solvent and tertiary amine from a carboxylic acid and an amine component, or an alcoholic component depending on the case under existence of 1,3,5-triazine. In this case As tertiary amine (2), ring type diamine or the addition product formed by becoming together with a triazine component from now on It is used by 0.30-1.10 of a desirable stoichiometric rate to a triazine component, the stoichiometric rates with; carboxylic acid, an amine component, or an alcoholic component are 0.2-5.0, and the mole ratios of a carboxylic acid and a triazine component are 0.5-1.5. As a carboxylic-acid component, amino acid, for example, the amino acid by which N protection was carried out, and a peptide correspond to this, and amino acid (C protection was carried out) or the peptide by which C protection was carried out corresponds to this as an amine component. As desirable 1,3,5-triazine, 2-chloro -4 and 6-dimethoxy-1,3,5-triazine (CDMT) are used, and the N and N'-dimethyl -1 and 4-piperazine are used as ring type diamine. Moreover, this invention is asked for protection of a patent of the addition product which consists of ring (2) type diamine and 1,3,5-triazine with said approach in which in the case of -80-+150-degree C temperature carries out under existence of an organic solvent and it deals. According to the approach by this invention, as compared with a well-known technical level, high yield is attained by short reaction time, and the amount of trash with few [clearly] tertiary amine bases arises.

[0040]

Said advantage of the approach by this invention is explained in full detail about the following example.

:

Example :

Example 1 (example of a comparison) :

THF10ml was inserted in in the 100ml three necked flask equipped with the thermometer, and 3.00 mil mol of 4-tertiary butyl benzoic acids was added to it. Next, N-methyl morpholine 3.05 millimol was dropped stirring into this mixture, and 2-chloro-4.6-dimethoxy-1,3,5-triazine 3.03 millimol (CDMT) was added successingly. Next, this mixture was stirred for 1 hour and benzylamine 3.0 millimol was dropped to this reaction mixture. Added dichloromethane 10ml and 10ml of 5% of citric-acid water

solutions after stirring of 16 hours, separated this phase successingly, 10ml of saturation sodium-hydrogencarbonate solutions and 10ml of water washed the organic phase one by one, it was made to dry with a sodium sulfate, and the solvent was removed after the filtration using a rotary evaporator. It was able to obtain with 67% of yield by using an N-benzyl-4-tertiary butyl benzoic-acid amide as a white solid-state.

[0041]

THF10ml was inserted in in the 100ml three necked flask equipped with the thermometer, and 3.00 mil mol of 4-tertiary butyl benzoic acids was added to it. Next, 1 and 4-dimethyl-piperazine 1.55 millimol was dropped stirring into this mixture, and 2-chloro-4.6-dimethoxy-1,3,5-triazine 3.03 millimol was added successingly. This mixture was stirred for 1 hour and benzylamine 3.0 millimol was dropped to this reaction mixture. Added dichloromethane 10ml and 10ml of 5% of citric-acid water solutions after stirring of 16 hours, separated this phase successingly, 10ml of saturation sodium-hydrogencarbonate solutions and 10ml of water washed the organic phase one by one, it was made to dry with a sodium sulfate, and the solvent was removed after the filtration using a rotary evaporator. It was able to obtain with 88% of yield by using an N-benzyl-4-tertiary butyl benzoic-acid amide as a white solid-state.

[0042]

example 3:

THF130ml was inserted in in the 500ml three necked flask equipped with the thermometer, and, subsequently to it, 30.0 mil mol of 4-tertiary butyl benzoic acids was added. Next, 1 and 4-dimethyl-piperazine 15.5 millimol was dropped stirring into this mixture, and 2-chloro-4.6-dimethoxy-1,3,5-triazine 30.3 millimol was added successingly. Next, this mixture was stirred for 1 hour and benzylamine 30.0 millimol dissolved in this reaction mixture into THF5ml was dropped.

Dichloromethane 130ml and 100ml of 5% of citric-acid water solutions were added after stirring of 16 hours, and this phase was separated successingly. Shook out the aqueous phase together with dichloromethane 100ml anew, 80ml of saturation sodium-hydrogencarbonate solutions and 45ml of water washed the organic phase by which uptake was carried out one by one, it was made to dry with a sodium sulfate after that, and the solvent was removed after the filtration using a rotary evaporator. It was able to obtain with the yield exceeding 99% by using an N-benzyl-4-tertiary butyl benzoic-acid amide as a white solid-state.

[0043]

example 4:

THF10ml was inserted in in the 100ml three necked flask equipped with the thermometer, and, subsequently to it, 3.00 mil mol of 4-tertiary butyl benzoic acids was added. Next, 1 and 4-diazabicyclo[2.2.2] octane 1.55 millimol was dropped stirring into this mixture, and 2-chloro-4.6-dimethoxy-1,3,5-triazine 3.03 millimol was added successingly. Next, this mixture was stirred for 1 hour and benzylamine 3.0 millimol was dropped to this reaction mixture. Dichloromethane 10ml and 10ml of 5% of citric-acid water solutions are added after stirring of 16 hours, and this phase is separated successingly. 10ml of saturation sodium-hydrogencarbonate solutions and 10ml of water washed the organic phase one by one, it was made to dry with a sodium sulfate after that, and the solvent was removed after the filtration using a rotary evaporator. It was able to obtain with 66% of yield by using an N-benzyl-4-tertiary butyl benzoic-acid amide as a white solid-state.

[0044]

example 5:

THF30ml was inserted in in the 100ml three necked flask equipped with the thermometer, and, subsequently to it, the 6.00 mil mol of pivalate was added. Next, 1 and 4-dimethyl piperazine 3.2 millimol was dropped stirring into this mixture, and 2-chloro-4.6-dimethoxy-1,3,5-triazine 6.5 millimol was added successingly. Next, this mixture was stirred for 2 hours and 2-phenyl ethylamine 6.5 millimol was gradually dropped to this reaction mixture. Dichloromethane 30ml and 50ml of 5% of citric-acid water solutions were added after stirring of 3 hours, this phase was separated successingly, and the aqueous phase was anew washed by 2x20ml of dichloromethanes. The solvent was removed for the organic phase by which uptake was carried out one by one 40ml of water, 50ml of saturation

sodium-hydrogencarbonate solutions, and after filtration 40ml of water washes again, make it dry with a sodium sulfate after that, and using a rotary evaporator. It was able to obtain with 90% of yield by using an N-phenylethyl-pivalate amide as a white solid-state.

[0045]

example 6:

Cooling in the solution with which 2-chloro [of dichloromethane 15ml Naka] -4 and 6-dimethoxy-1,3,5-triazine 2.66g (CDMT) and Boc-Ser-OH3.32g (BOC-serine: M= 205.21) were stirred, with the dropping test, 1 and 4-dimethyl piperazine 7.65 millimol was added, as it was while internal temperature is -5-0 degree C. Next, stirring was made to continue at 0 degree C until all CDMT(s) reacted (about 1 hour). next, this reaction mixture -5-0 degree C -- dichloromethane 7.5ml -- inner H-Val-OBzl*p-tosylateg [5.69] (valine benzyl ester-p-toluene sulfonate: M= 379.48) and 1 and 4-dimethyl piperazine 0.89g was added with the dropping test, and it stirred at 0 degree C after that for further 2 hours. after that -- a room temperature -- 14 hours -- stirring -- succeedingly -- a solvent -- a rotary evaporator -- removing -- the residue -- ethyl-acetate ester 45ml -- it put into inside. Next, 15ml of water washed the generated suspension one by one on water of 15ml, 15ml of 10% of citric acids, 15ml of water, 15ml of saturation sodium-hydrogencarbonate solutions, and the last target. Finally dried the organic phase on magnesium sulfate, filtered after that, and it was made to condense in a vacuum, and was made to recrystallize [petroleum ether / ethyl-acetate ester /]. The product was able to be obtained with 85% of yield.

[0046]

example 7:

4-tertiary butyl benzoic-acid 6 millimol in THF20ml and CDMT6.06 millimol were inserted in in the 100ml three necked flask, and the 3.1 mil mol of dimethyl piperazines was dropped, stirring into this mixture. Methanol 20ml was added after 1 hour, and this mixture was stirred for 16 hours. Then, the solvent was distilled off, 20ml of methylene chlorides was added to the obtained residue, and it shook out together with 5% of citric acid. 30ml of saturation sodium-hydrogencarbonate solutions washed the organic phase first, 30ml of water washed succeedingly, next it was made to dry with a sodium sulfate, and the solvent was distilled off after filtration. In this way, desirable ester was able to be obtained with 85% of yield.

[0047]

example 8:

THF10ml was inserted in in the 100ml three necked flask equipped with the thermometer, and, subsequently to it, the 3.00 mil mol of tertiary butyl benzoic acids was added. 1 and 4-dimethyl piperazine 3.05 millimol was dropped stirring into this mixture, and 2-chloro-4,6-dimethoxy-1,3,5-triazine 3.03 millimol was added succeedingly. This mixture was stirred for 1 hour and benzylamine 3.0 millimol was dropped to this reaction mixture after that. Dichloromethane 10ml and 10ml of 5% of citric-acid water solutions were added after stirring of 16 hours, and this phase was separated succeedingly. 10ml of saturation sodium-hydrogencarbonate solutions and 10ml of water washed the organic phase one by one, it was made to dry with a sodium sulfate after that, and the solvent was removed after the filtration using a rotary evaporator. It was able to obtain with 93% of yield by using such an N-benzyl-tertiary butyl benzoic-acid amide as a white solid-state.

[0048]

Discussion :

In relation to yield, using N-methyl morpholine (example of comparison 1 reference) above all as compared with the well-known approach and direct, lessons is taken from the example of the tertiary butyl benzoic acid as a carboxylic-acid component or an amine component, and the coupling reaction of benzylamine, respectively, and the arete of this approach in comparison with a well-known synthesis method is just shown. namely, when well-known system"CDMT (1.01Eq) / N-methyl morpholine (1.017Eq)" are used When 67% of yield is only attained (example of comparison 1 reference) and the coupling system by CDMT (1.01Eq) and 1 which decreased clearly, and this invention which consists of a 4-dimethyl-piperazine (0.517Eq) is used unlike this 88% of yield raised remarkably can be attained

(Example 2), and when an addition technique is changed and the after treatment in the inside of the increased amount of batches is optimized, in addition, it can be made to go up so that it may exceed 99% rather (Example 3).

[0049]

Therefore, when this coupling system which consists of 1,3,5-triazine and ring type diamine with the economical advantage of trash, for example, few amounts of a base, and the optimized atomic economical efficiency was used, it was generated at the chemical effectiveness at which the coupling system has also been improved. Additionally, i.e., conversion already quantitative after the reaction time of 1 hour (following), by which reaction time was able to be shortened remarkably is observed. When ring type diamine, 1, 4-dimethyl piperazine, and 1.017Eq are used instead of 1.017Eq of N-methyl morpholines of a well-known technical level (example of comparison 1 reference), 93% of yield which rose is attained instead of 67% of yield (example 1 of a comparison) like a well-known technical level (Example 8).

[0050]

However, a coupling reaction advances very efficiently, when another (2) ring type diamine which has the 3rd amino group, respectively is used as a 1 and 4-dimethyl piperazine. That is, when diamino bicyclo [2.2.2] octane (DABCO) is used, a desirable coupling product can be obtained with 66% of yield (Example 4). It also proves that a new coupling reagent can use Example 5 efficiently because of coupling of aliphatic carboxylic acid (yield: 90%). Moreover, the proposed approach is suitable for coupling of the amino acid which is not protected advantageously, the amino acid by which N protection was carried out, or the ***ing peptide. In this case, an important thing is that existence of an additional functional group is attained as rather proved by Example 6. That is, in composition of the coupling product which leaves BOC-Ser-OH and H-Val-OBzl, coupling using a new system advances at the high effectiveness in 85% of yield (Example 6).

[Translation done.]